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DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

NA	1b. RESTRICTIVE MARKINGS: NA
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE: NA	3. DISTRIBUTION / AVAILABILITY OF REPORT: Distribution Unlimited
4. PERFORMING ORGANIZATION REPORT NUMBER(S): NA	5. MONITORING ORGANIZATION REPORT NUMBER(S): NA
6a. NAME OF PERFORMING ORGANIZATION: University of Wisconsin; 6b. OFFICE SYMBOL (If applicable): NA	7a. NAME OF MONITORING ORGANIZATION: Office of Naval Research
6c. ADDRESS (City, State, and ZIP Code): Department of Chemical Engineering, 1415 Johnson Drive, Madison, WI 53706	7b. ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street, Arlington, VA 22217-5000
8a. NAME OF FUNDING / SPONSORING ORGANIZATION: Office of Naval Research; 8b. OFFICE SYMBOL (If applicable): ONR	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: N00014-89-j-3001
8c. ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street, Arlington, VA 22217-5000	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 61153N; PROJECT NO. RR04106; TASK NO. 4412068; WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
(U) Microstructural Models of Interactions that Govern Protein Conformations

12. PERSONAL AUTHOR(S)
Kim, Sangtae

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 7/89 TO 6/90	90 May 31	5

16. SUPPLEMENTARY NOTATION
None

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Tertiary structure, lysozyme, rotational diffusion coefficient, translation diffusion coefficient
06	03		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A methodology for calculating hydrodynamic friction coefficients for globular proteins of complex shape is described and applied to the calculation of rotary and translation diffusion coefficients of lysozyme. The new algorithm is stable with respect to geometrical complexity and amenable to iterative solution on parallel computers. Our current work clarifies the role of three sets of assumptions: (1) Assumptions associated with the generalized Stokes-Einstein theory; (2) Assumptions on how to generate an appropriate surface (using atomic coordinates) to use in the theory; (3) Assumptions on how to calculate the mobility of a rigid body defined by a molecular surface.

Plans for next year include: (1) computations involving internal motions, on high-performance parallel computer architectures; and (2) simulation of folding of protein fragments. Both efforts are planned as first steps in describing the tertiary dynamics from interactions between secondary structures.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	(U)
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DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

S/N 0102-LF-014-6603

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

90 07 25 085

ANNUAL PROGRESS REPORT

GRANT #: N00014-89-j-3001 R&T Code: 4412068

PRINCIPAL INVESTIGATOR: Sangtae Kim

INSTITUTE: University of Wisconsin - Madison

GRANT TITLE: Microstructural Models of Interactions that Govern Protein Conformations

PERIOD OF PERFORMANCE: 1 July 1989 - 31 May 1990

OBJECTIVE: To apply computational methods for microstructures suspended in a viscous fluid to the calculation of the slower dynamic processes in protein folding. The concerted motion of the entire tertiary structure will be considered with the secondary consituents modeled as solid segments. The short term objective is to determine diffusion/friction coefficients, first, for the overall protein and then for the larger sub-structures.

ACCOMPLISHMENTS (last 12 months): My students and I have completed the interfacing of the Brookhaven Protein Database to our simulation code for the hydrodynamic mobility/friction factor, the Completed Double Layer Boundary Integral Equation Method (CDL-BIEM). The key step was accomplished by converting M.L. Connolly's Molecular Surface Package (Piecewise Quartic Molecular Surface, Surface Rendering by Foliation, Triangulation by Recursive Bisection) into a boundary element mesh generator for CDL-BIEM. This process creates realistic three-dimensional rendering of surfaces of smaller protein residues using about 300 boundary elements. An entire enzyme such as lysozyme (Figure 1) can be rendered using about 3000 boundary elements.

For N boundary elements, the CDL-BIEM calculation involves the iterative solution of a $3N$ by $3N$ dense linear system, as discussed in our publication [1]. For compact, sphere-like shapes, the Jacobi iteration of the form, $x = Mx + b$, converge very quickly, in as few as five iterations. For more complex shapes associated with tertiary structures of globular proteins, the procedure converges too slowly. We have implemented more powerful iterative methods based on the residual reduction methods of Eisenstat *et al.* (SIAM J. Numerical Analysis **20**, pp. 231-154, 1983). Typical convergence behavior of the mobility coefficient (which is directly proportional to the diffusion coefficient) is shown in Figure 2 for a fairly difficult but representative problem from the viewpoint of numerical analysis: a composite object formed by joining a thin rod with a sphere.

The largest system attempted to date involved the calculation of the mobility/diffusion coefficient (or equivalently, the friction factor) of lysozyme, using the shape obtained from the Brookhaven protein database. With about 3000 triangular boundary elements, the resulting linear system of equations is 9000 by 9000. Using a memory-saving version in which the matrix elements are recalculated as needed, an iteration takes about 10 hours on a super-minicomputer running at 10 MFlops, and a complete calculation requires about

10 iterations. In other words, a Gigaflop computer will be able to perform the entire calculation in about 1 hour.

SIGNIFICANCE: It is well known that there is a systematic pattern of deviation between the theoretical predictions and experimental measurements of diffusion coefficients as a function of protein shape. The more simple, spherical shapes are adequately explained by theories based on the hydrodynamic radius and the radius of gyration. The 'outliers' are invariably those proteins with contorted surface shapes. The CDL-BIEM calculations show great promise in predicting both translational and rotational diffusion coefficients of these difficult proteins from first principles.

The significance of predicting protein diffusion coefficients using CDL-BIEM lies in the fact that we will be able to test the Stokes-Einstein theory without making any assumptions on how to calculate the mobility of the rigid bodies we use to model the proteins. Past calculations of diffusion coefficients have relied on three sets of assumptions:

1. Assumptions associated with the generalized Stokes-Einstein theory.
2. Assumptions on how to generate an appropriate molecular surface (using the given atomic coordinates) to use in the theory.
3. Assumptions on how to calculate the mobility of the rigid body defined by the molecular surface.

We can eliminate the third set of assumptions, thus shedding light on the first two sets. Since the first two are also involved in the more complicated problem of protein folding (or dynamics of internal motions) we gain information of use in future calculation of these motions.

WORK PLAN (next 12 months): The objective next year is to move our work to a new generation, GigaFlop computer architecture, featuring many processors (supercomputers-on-a-chip) running in parallel, to be located in the new Center for Parallel Computational Engineering, UW-Madison. Our iterative methods are highly parallel and should achieve close to the theoretical speedups in a multi-processor environment. Runs on the IBM 3090, Sequent Symmetry and the Intel iPSC/860 have all confirmed this expectation.

PUBLICATIONS TO DATE:

1. A theoretical paper (submitted before the contract was awarded) has appeared.

   Karrila, S.J., Fuentes, Y.O. and Kim, S. (1989) Parallel computational strategies for hydrodynamic interactions between rigid particles of arbitrary shape in a viscous fluid, J. of Rheology **33**, 913-947 (copy enclosed).

2. An abstract was recently submitted to the session on ***Molecular Biophysics of Proteins, Peptides and Polynucleotides***, chaired by M.L. Yarmush, in the 1990 national meeting of the American Institute of Chemical Engineers (copy enclosed).

   Kim, S. and Brune, D.A. (1990) Theoretical predictions of translational and rotational diffusion coefficients of proteins. Abstract.

Figure 1. Triangulation of lysozyme for the boundary element calculation of the friction coefficients.

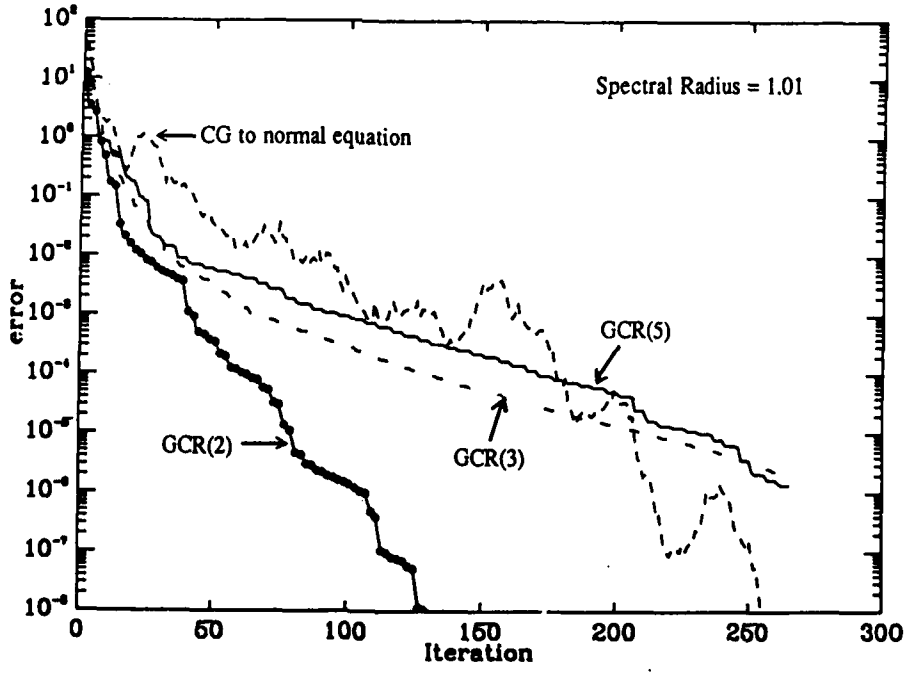
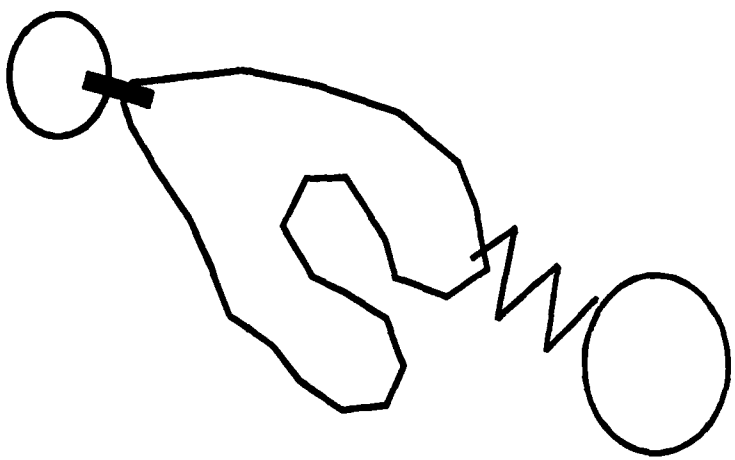


Figure 2. Convergence of the generalized conjugate residual method of Eisenstat *et al.* as compared to the conjugate gradient method applied to the normal equations.

Highlights: Microstructural Models of Interactions that Govern Protein Conformations



Objectives

- Develop computational methods for tertiary level interactions in proteins
- Determine applicability to protein folding at the tertiary level

Accomplishments

- Generation of boundary elements starting from Brookhaven databank
- New computational method tested on uniprocessors and parallel computers
- Accelerated convergence achieved using residual reduction methods

Significance

- Friction factors (mobilities) determined from surface geometry without *a priori* hydrodynamic approximations

S. Kim, UW-Madison; 1990

ANNUAL REPORT QUESTIONNAIRE

Principal Investigator: Sangtae Kim

Institute: University of Wisconsin-Madison

Grant title: Microstructural Models of Interactions that Govern Protein Conformations

Period of performance: July 1, 1989 - May 31, 1990

Number of publications last year: 5

Number of patents/inventions: 0

Total number of students/trainees: 7

How many are female? 2

How many are minority students (e.g. Black, Hispanic)? 2

How many are not US citizens? 4

Awards/Honors to PI and/or to members of PI's research group (please describe):

S. Kim	1989 Allan P. Colburn Memorial Lecture, U. of Delaware
S. Kim	Distinguished Visiting Scholar, U. of Massachusetts
S. Kim	H.I. Romnes Faculty Fellow, U. of Wisconsin
G.A. Huber	National Science Foundation Fellowship

Equipment purchased (# and description of items >$1500): None

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